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Measles resurgence in Argentina: 1997–8 outbreak

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SUMMARY

Epidemiological and clinical findings from 1162 serologically confirmed measles cases occurring in Buenos Aires, Argentina in 1997 and 1998 were retrospectively reviewed. From 90 hospitalized children, measles virus was detected by direct RT–PCR from nasopharyngeal secretions. Patients were grouped as follows: (i) not vaccinated: infants < 12 months; (ii) regularly vaccinated: children 1–4 years not covered by the last catch-up; (iii) catch-up vaccinated: patients 5–19 years immunized during the 1993 campaign. Most cases were recorded in non-vaccinated infants (54%), and the lowest in catch-up vaccinated children (16%). Mean age of the 90 hospitalized children was 11·3 months. Pneumonia was the major hospitalization cause followed by pneumonitis. Two children required intensive care and one died. The 1993 catch-up campaign seemed to reduce the number of cases in the 5- to 19-year-old group. Lack of timely follow-up probably led to the accumulation of susceptible individuals allowing measles re-emergence. Direct viral detection by RT–PCR proved to be a sensitive tool for molecular epidemiology surveillance.

INTRODUCTION

Measles is one of the major infectious causes of mortality worldwide [1]. Since the inception of the World Health Organization's Expanded Program on Immunization in 1974, the number of fatal cases has declined globally from 5·8 million in 1980 to 1·1 million in 1995 [2, 3]. Prior to the development of the measles elimination strategy, outbreaks usually recurred every 3 years, but with the widespread use of measles vaccine, the period has lengthened and the number of cases has decreased. In most countries in the American continent, a 99% reduction in incidence has been reported compared to the pre-vaccine era. The OMS-OPS Pan American Health Organization Measles Elimination Program includes laboratory surveillance and 3 vaccination strategies: (i) catch-up: one-time vaccination campaign, targeting all the children aged from 9 months to 14 years, regardless of measles disease history or vaccination status; (ii) keep-up: routine services, with a coverage greater than 90% of each successive birth cohort; and (iii) follow-up: vaccination campaigns conducted every 2–5 years targeting children aged 1–4 years [4, 5]. In Argentina, despite including in regular schedules one-dose measles vaccination since 1978 and Measles–Mumps–Rubella vaccine since 1997, measles virus has caused many outbreaks. The registered number of cases of the last two major outbreaks was 29102 in 1984 and 42093 in 1991. After the 1991 outbreak, a catch-up measles vaccination strategy was applied in June 1993, reaching a 96·5% coverage rate country-wide [6]. The current outbreak began in October 1997 with more than 15000 confirmed and 58 fatal cases.

In this study, epidemiological data and hospitalized children's clinical findings were reviewed retrospectively. Direct viral detection as a tool for

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molecular epidemiology surveillance in developing countries is discussed.

METHODS

Measles case definitions

A measles case was defined as fever higher than 38 °C, erythemathous maculopapular rash, coryza and/or cough and/or conjunctivitis. Patients with measles-specific IgM antibodies were included in this study.

Epidemiological and clinical data

Children were recruited in the Emergency Room or Physician's Office at the Ricardo Gutiérrez Children's Hospital from October 1997 to October 1998. For each patient, an epidemiological record was made including age, date of rash onset, vaccination status, address and source of case exposure. Most cases came from diverse Buenos Aires suburban areas. Medical records of 90 inpatients admitted for measles to the Infectious Diseases Unit 10 at the Ricardo Gutiérrez Children's Hospital were retrospectively reviewed. Children were grouped for the analysis as follows: (i) not vaccinated: Infants below 12 months; (ii) regularly vaccinated: children 1–4 years of age not covered by the last catch-up because they were too young. However, these patients should have received at least the regular 12-month one-dose measles vaccination and (iii) catch-up vaccinated: 5–19 years patients, immunized during 1993 campaign.

Pneumonia and pneumonitis were defined by clinical and radiological findings. Pneumonia has crackling rales and classic signs of consolidation and pneumonitis was characterized by a diffuse infiltrate, especially in the perihiliar areas.

Virological studies

Serum samples were obtained soon after maculopapular rash onset and measles diagnosis was confirmed by IgM-indirect fluorescence antibody (IFA) detection [7]. A second serum sample was required if the sample was obtained 72 h before the rash onset. Nasopharyngeal secretions or plasma samples (only from two patients) were also collected from hospitalized children and total RNA was isolated by the acid guanidinium–thiocyanate–phenol method [8]. RT–PCR was directly performed with specific haemagglutinin-gene primers [9]. Serial dilutions of Schwarz measles vaccine strain were made to amplify from 10^4 to 1 $TCID_{50}$. The 377-bp products were visualized by ethidium bromide staining in 2% agarose gel.

RESULTS

Epidemiological data

Case distribution per month in the 1997–8 outbreak is shown in Figure 1. Cases were detected throughout the period and transmission was not interrupted in summer. However, over a tenfold increase was recorded in winter (June–September). The age distribution for the outbreak is shown in Figure 2. Although the age at which vaccination was given was lowered from 12 to 6 months in August 1993, most cases occurred in the infant group, 87% being 6–11 months of age. Children aged from 1–4 years (second group) should have been covered with at least one dose, but 38% failed to receive the obligatory vaccine. School-aged children aged 5–19 years (third group) showed the lowest number of cases although 14% were not covered despite the massive catch-up campaign. The age-specific incidence per 100000 was 2150 for infants below 1 year; 947 for children of 1 year; 219 for the 2–4 years age group; 125 for the 5–9 years age group; 53·3 for the 10–14 years age group; 37·9 for the 15–19 years age group; 64·6 for the 20–29 years age group; 27·3 for the 30–39 years age group; and 2 for the 40–80 years age group (Forlenza R, personal communication).

Inpatients clinical findings

During this outbreak, 20% of confirmed cases were hospitalized. From 90 inpatients analysed, 6 (6·67%) were aged 0–3 months, 18 (20%) 4–6 months, 20 (22·22%) 7–9 months, 26 (28·89%) 10–12 months, 7 (7·78%) 13–15 months, 4 (4·44%) 16–18 months, 3 (3·33%) 19–22 months, 3 (3·33%) 29–31 months and 3 patients were aged 36, 41 and 72 months. Few cases were found during the first months of life but a remarkable increase was shown from 4 to 12 months of age. Beyond 13 months the number of inpatients declined. The mean hospitalization age was 11·3 months (range 23 days–72 months).

Mean hospitalization period was 5·5 days (range 1–22 days). Clinical parameters at admission showed that pneumonia was the major cause followed by pneumonitis. In 3/90 (3·3%) patients, additional

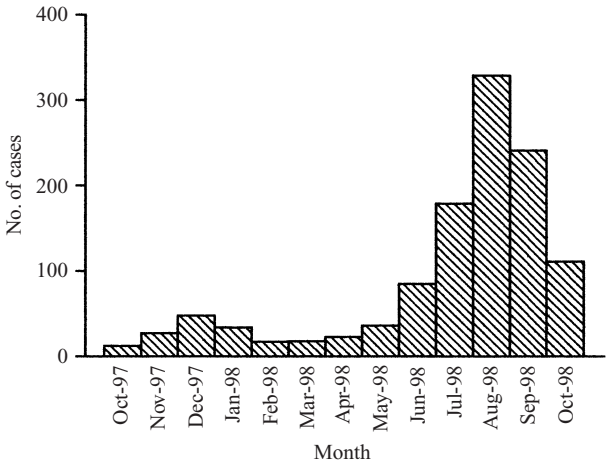

Fig. 1. Measles case distribution per month throughout the 1997–8 measles outbreak. Distribution of the 1162 measles cases from October 1997 to October 1998 is shown.

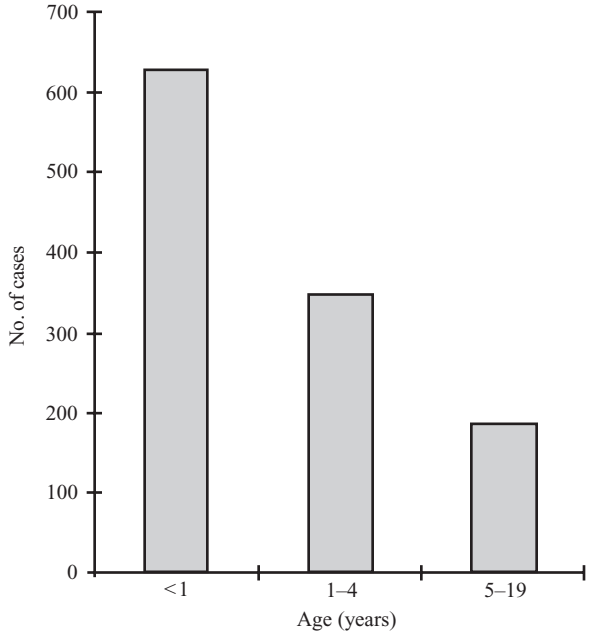

Fig. 2. Age distribution throughout the 1997–8 measles outbreak. Age distribution of the 1162 measles cases is shown. According to vaccination status, children were classified as (i) non-vaccinated: infants < 1 year; (ii) regularly vaccinated: children 1–4 years; and (iii) catch-up vaccinated: children 5–19 years.

diagnoses such as Kawasaki syndrome, sepsis and hypotonic child syndrome were recorded. One patient showed hepatomegaly and spleen enlargement. In some cases more than one cause of admission was recorded. In 47/90 patients supplementary oxygen was required for an average of 3·2 days (range 1–6 days). Two patients developed acute respiratory distress syndrome requiring mechanical ventilatory

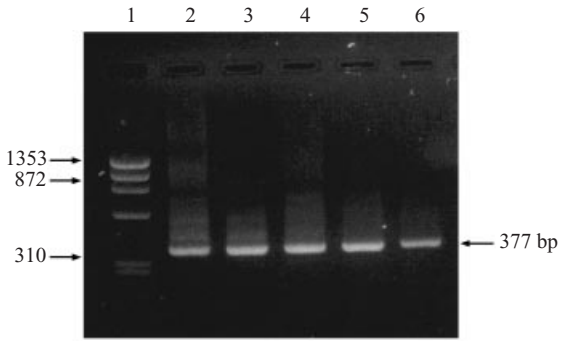

Fig. 3. Measles haemagglutinin RT–PCR sensitivity. Lane 1, molecular weight marker; lane 2, 10^4; lane 3, 10^3; lane 4, 10^2; lane 5, 10; lane 6, 1 $TCID_{50}$, respectively.

support. One of them, an 11-month-old boy was admitted to intensive care with measles pneumonitis, followed by irreversible respiratory failure. The second one, a 3-month-old boy, developed bronchiolitis requiring critical care for 3 days.

Virological data

From 1835 probable measles cases, 1162 (63%) were confirmed as acute measles by measles-specific IgM detection. Measles virus RNA was amplified in all hospitalized cases by RT–PCR. The 377-bp PCR product obtained from serial dilutions from 10^4 to 1 $TCID_{50}$ was visualized (Fig. 3) showing that at least 1 $TCID_{50}$ from nasopharyngeal aspirates could be detected. PCR product was detected whether nasopharyngeal secretions were left for 1–6 h at room temperature or stored at -20 °C for 1–3 months. Measles RNA was amplified from plasma samples obtained 14 days after onset of maculopapular rash. Plasma samples were processed only when nasopharyngeal secretions were not available (two cases). This PCR product proved adequate for further sequence analysis and showed that, despite some variations, all viruses belonged to D6 group, epidemiologically linked to 1997 Brazil outbreak [10].

DISCUSSION

Although measles natural infection confers lifelong immunity, antibodies induced by one-dose measles vaccination decrease with time. Epidemiological data of the current outbreak showed that 54% of cases were below 1 year of age. Infants become susceptible due to the drop in maternal antibodies from the third to the sixth month of life [11–14]. Many mothers were born after 1978, when the one-dose measles vac-

cination scheme was implemented. These young mothers may not have enough antibodies to protect their infants beyond the first months of life. The presence of a considerable number of susceptible adults, who had neither natural measles infection nor measles vaccination, has contributed to the re-emergence of measles [15]. Pre-school-aged children accounted for 30% of cases. Many reasons such as non-optimal or regional variations in regular coverage; lack of a timely follow-up vaccination campaign; and vaccine non-responders led to a rapid accumulation of susceptible children within this group. Our results are similar to the measles age distribution in developing countries prior to large-scale immunization [16]. On the other hand, in developed countries with populations having high rates of coverage, measles incidence is delayed to school-aged children and adults with at least one dose of measles vaccine [17–19].

The mistaken perception that measles is a mild illness hinders its elimination [3]. Despite the availability of an effective vaccine, measles complications, such as respiratory tract involvement and encephalitis, remain major causes of hospitalization in developing countries [20]. The differential diagnosis between Kawasaki disease and some clinical presentations of measles can prove troublesome [21]. Only one fatal case was recorded during this study, which is in agreement with previously calculated measles mortality of 1–17/1000 cases [22].

When used appropriately with standard epidemiology, molecular surveillance is a major component of the Measles Elimination Program [23, 24]. Genetic characterization of measles virus may contribute to the determination of the geographical sources of outbreaks, transmission pathways and control strategy assessment. Although this outbreak was epidemiologically linked to the 1997 Brazil outbreak, inter- and intra-epidemic variations were registered and are being explored. Molecular detection sensitivity depends on viral recovery from clinical samples. In countries with large territories, viral viability preservation represents an obstacle. RNA has been recovered despite the poor quality of sample preservation. PCR product was detected whether nasopharyngeal secretions were left at room temperature or stored at -20 °C. Even plasma samples, obtained if nasopharyngeal secretions were not available or later after maculopapular rash onset, were amplified. Early detection by RT–PCR seemed not to be affected by these disadvantages.

The aim of follow-up strategy, to achieve and maintain high levels of measles immunity among infants and children has been reached neither in our country nor in others [3, 4, 6]. The only feasible measure to be taken during an outbreak in order to protect the 6–11 months old group is to lower the vaccination age to 6 months. Unfortunately, this strategy was only recently applied. According to our data measles eradication still poses a considerable challenge to developing countries.

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